

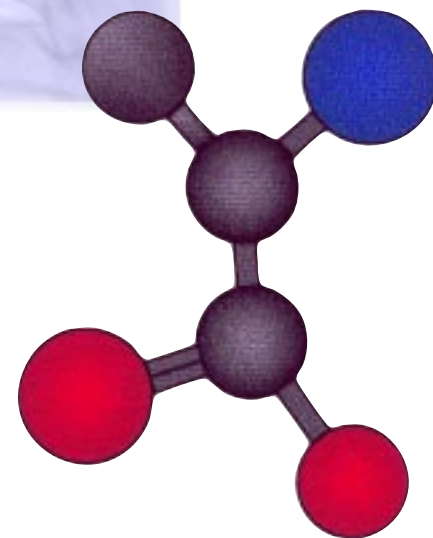
NEW BIOCATALYSTS:

ESSENTIAL TOOLS FOR A SUSTAINABLE 21st CENTURY CHEMICAL INDUSTRY



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The authors thank the planning group and participants in the workshop for their many suggestions and careful review of the several drafts. Special credit is due Brian Davison and David Boron for their contributions and graphics.

Technical assistance by Mary Donahue, graphic designer, and Georgia Herod, editor, was superb. Pamela Garcia served as the workshop secretariat and did an excellent job in a complex organizational task.

Finally, we wish to thank you, our reader, for your attention and ask that you join us in working toward making biocatalysts all they can be.

*William H. Scouten
Gene Petersen*



About the cover . . .

The design of this report was based on the ideas of a “new generation” and sustainability, along with the use of the core structure of an amino acid (creative child’s play and serious science), a motif used throughout the interior of the report.

The cover photos represent the past chemical industry (chemical plant), the hopes of a greener industry (plants in field) and the future (a young child with a “molecular structure.”) Our model, Liam, was born in March of 1999 and is 1 1/2 years old at the time this report is published. He represents the next generation who will benefit from our efforts.

This report seeks to define vision and strategic plans for the chemical industry into the year 2020, the same year Liam will be 21 years old.

(photos courtesy of National Renewable Energy Lab and Mary Donahue.)

Background

This report represents the November, 1999 workshop efforts and subsequent contributions of 50 leading scientific and industry experts in biocatalyst use and development. The goal was to produce a “roadmap,” or strategic plan, for developing and utilizing a new generation of biocatalysts for the 21st Century. The focus of the work group was on the very complex chemical industry and such chemistry-related areas as the pharmaceutical and environmental sciences.

Biocatalyst technology, as a part of a broader “chemical biotechnology,” is increasingly important as a tool for chemical synthesis. Its application is driven by consumer demand for new products and by industrial attempts at increasing profits and cost reduction, as well as government and regulatory pressures and new technologies and scientific discovery. Current applications of biocatalysts include the production of high fructose corn syrup, aspartame, semi-synthetic penicillins and award-winning cancer drugs.

Despite these examples of biocatalyst applications, biocatalysts cannot reach their potential without a concerted effort on the part of industry, non-profit and government funding agencies, and academic and national lab scientists. The contributors to this plan defined the goals needed to reach this potential, analyzed technical barriers and problems to be surmounted, and formulated an initial plan to implement the resulting program.

Goals

Biocatalyst program goals include traditional chemical industry goals to reduce material, water and energy consumption and pollutant dispersal by 30% in the next two decades. More specifically, with respect to biocatalysts, the goals include:

- developing biocatalysts which are better, faster and cheaper than current chemical catalysts
- development of a tool box of biocatalysts, i.e., biocatalysts that can catalyze a broader range of reactions and have greater versatility than is now possible
- increased temperature stability, activity, and solvent compatibility
- developing molecular modeling to permit rapid *de novo* design of new enzymes
- creating better tools for new biocatalyst development
- educating the public to the societal benefits of using and creating biocatalysts

Barriers to overcome

Technical barriers to be overcome include:

- a limited knowledge of enzyme/biocatalyst mechanisms
- poor understanding of metabolic pathways for secondary metabolites, including pathway interactions
- a limited number of methods to engineer whole organisms, i.e., metabolic engineering
- the high cost of producing many enzymes and co-factors for biocatalyst application

Implementation

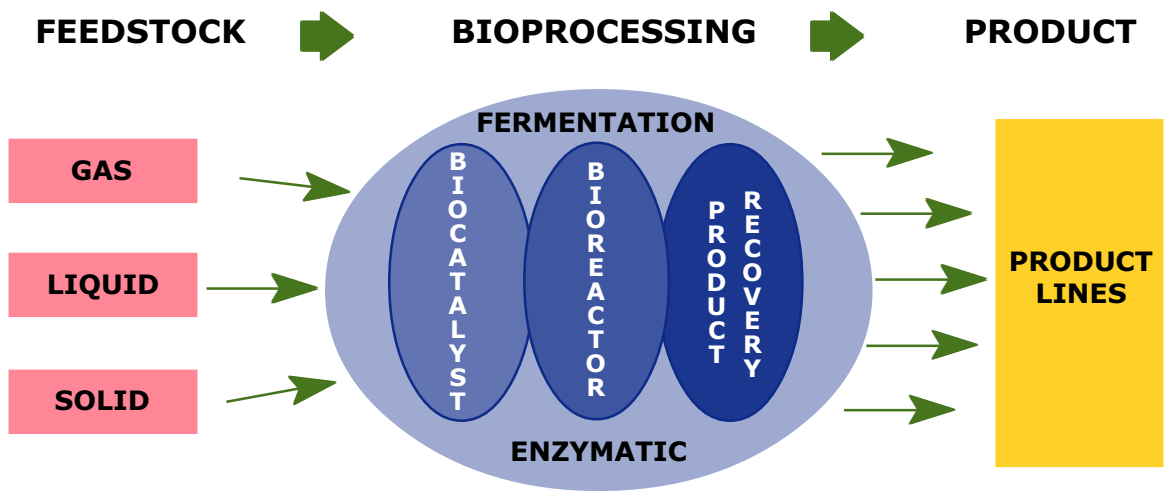
The goal of the implementation efforts is to increase the awareness of various constituencies as to the value and benefits of the study and development of new and more efficient biocatalysts. Specific activities will include:

- developing performance indicators for evaluating the success of these efforts
- establishing an executive steering committee for monitoring and promoting the development and use of biocatalysts
- presenting the roadmap to appropriate trade organizations and professional societies
- increasing the awareness of the value that biocatalysts can have commercially to industrial leaders and appropriate federal agencies
- promoting an understanding of the opportunities and challenges of biocatalyst development by basic scientists and the agencies which fund them

Conclusion

Substantially increased emphasis on biocatalyst development is an important goal for chemistry-related industries. This needs to be supported by a broad and concerted effort by those who understand the opportunities and challenges that the creation of a new generation of environmentally friendly, profitable and diverse biocatalysts will bring. All groups concerned—consumers, industrialists, environmentalists and scientists, to name a few—will benefit in a very significant way.

A Feedstock-Driven Systems Approach to Roadmapping Biotechnology



FEEDSTOCK

- Gas
 - Syn Gas
 - CO₂
 - Organic Vapors
- Liquid
 - Organic
 - Sugar Solution
- Solid
 - Biomass
 - Consumer Waste

BIOPROCESS

- Immobilized Enzymes
 - Ambient to Extreme
- Fermentation
 - Immobilized
 - Free Cell
 - Ambient to Extreme
- Reactors
 - Continuous Systems
 - Membrane
 - Batch or CSTR
- Separation
 - In situ*
 - Secondary
- Media
 - Gaseous
 - Aqueous
 - Organic

MARKET

- Pharmaceutical
- Fine Chemicals
- Specialty Chemicals
- Feedstock
- Bulk



Why Have a Bioprocessing/Biotechnology Work Group and a Biocatalysis Strategic Plan?

This report represents the work of over 50 leading scientific and industry experts in biocatalyst use and development who attended a two-day workshop in November, 1999, as well as subsequent contributions. The goal of the workshop was to produce a “roadmap,” or strategic plan, for developing and utilizing a whole new generation of biocatalysts for the 21st Century.

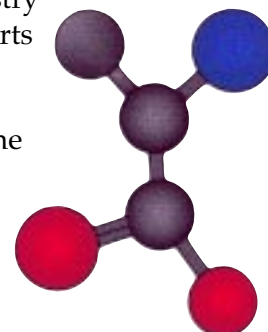
A summary of the results of this conference is outlined in the Executive Summary and detailed in Section III of this report. The present section seeks to describe the setting in which the conference took place. Of particular importance are these questions:

- “Why do we have a work group on bioprocessing and biotechnology as part of the chemical industry’s ‘visioning,’ or strategic planning, process?” and
- “Why do we begin with a plan for developing ‘new biocatalysts’ as the first output from the workgroup?”

To understand this, we will first begin with a sketch of the Vision 2020 process in the chemical industry and relate a little about the complexity of the industry with the aim that the reader will sense both the significance of the process and the difficulty of the task. Finally, we will outline the results of the workshop and the conversation within the industry that we hope, and expect, will follow.

Nature of the chemical industry

The chemical industry is both diverse and complex and the entire “chemical enterprise,” consisting chiefly of industry, academics, and federal and national laboratories, possesses even greater diversity. All three major sectors do basic research, applied research, and development in varying degrees, depending on the philosophy and objectives of the particular company, organization or institution. This is certainly true for catalysis, in general, and biocatalysis, in particular. Typically, industry carries out more of the development and deployment efforts while academics tend to focus on the basic research problems. However, no absolute division of “who does what” exists as industry conducts its own basic research and some universities and federal laboratories often carry out precompetitive R&D designed to enhance or lead to commercial applications.



This diversity within the chemical enterprise enhances the economy and security of the country. The Chemical Manufacturers Association reports that the \$419 billion industry produces over 70,000 products and employs over one million persons. The industry, one of the top three exporting industries in the country, strengthens our worldwide competitiveness. This performance doesn't even include the pharmaceutical industry that is, in many ways, an applied area of chemistry. This fine chemical industry faces many of the same research needs as commodity chemicals but has more involvement in biocatalysis and biocatalysts.

Environmental issues are very important to the industry. Reducing pollution has been a major concern leading to the development of a whole new mindset based on "green chemistry," that is, chemistry which is friendly to the environment, minimizes waste, reduces energy utilization and often favors renewable resources over petroleum-based feedstocks. A major goal, then, for research in the industry is the development of processes and products that minimize waste, CO₂ emissions, and energy utilization. The sustainable uses of our resources, whether fossil-based or biobased renewables, is a consideration in the chemical industry and enterprise.

"Chemical biotechnology" is the rapidly growing application of biotechnology to chemical production. It often goes hand-in-hand with green chemistry and the use of renewable feedstocks. Other applications of biotechnology lead to new products, new manufacturing methods and improved economics with lesser demand for energy, or fewer negative or deleterious impacts on the environment.

Chemical biotechnology has made a big impact in the industry structure as firms have been acquired, divested, and restructured around various biochemical innovations. Biotechnology is very pervasive in the food industry — e.g., enzymes for starch manufacturing, beverage production, meat preservatives, etc. Many more impacts in the food industry are certain to come from use of biotechnology. A high level of uncertainty exists in biotechnology relative to recombinant foods and the impact of genetic engineering on crops, but much of this uncertainty is being addressed with facts and information that demonstrate food safety and safe practices in farming in the U.S. The perceptions abroad are not as favorable. Pharmaceutical use of biotechnology is virtually assured; even though policy issues related to biomaterials, textiles and similar products have yet to be addressed, these areas seem to be on a reasonably firm base.

In the past, initial reactions led to great caution in applying recombinant DNA technology to real world problems. This caution has subsided as understanding of the technology's benefits has increased. Similarly, the use of biotechnology in industry may go through a cautious phase only to blossom as a new, and even more widely accepted, positive force for mankind. Indeed the history of the entire Industrial Revolution may be looked upon as a model for the future of the biotechnological revolution.

This strategic plan or “roadmap” is one of several that have or will be prepared to address key areas of research in the chemical industry. This contrasts with the visioning process in other industries, e.g., aluminum or glass, where a single visioning process and a single roadmap may easily suffice to describe the most relevant research needs, and barriers, in the industry.

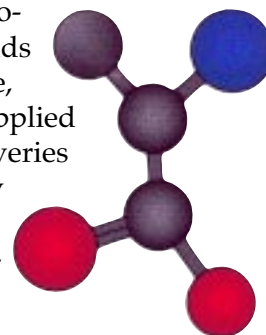
The difference, of course, is that the chemical industry is very unlike such monolithic industries as aluminum or glass. Indeed, “chemicals” consists of both small companies with a limited number of products and a smaller number of large multi-national companies with hundreds of products, processes and intermediates. The relationship between chemical companies is often symbiotic with suppliers supplying end users, intermediate producers or even their own suppliers. Some companies even integrate their feedstock supply, production, and use functions. However, the greatest majority of companies operate in the horizontal industrial mode and maximize their capabilities and strengths in their own niches in order to produce a slate of products which they can sell.

Visioning for the chemical industry is further complicated by the problem of definition. Should petrochemicals be included? Are agriculturally derived chemicals a product of the chemical industry? And while pharmaceuticals are really “fine chemicals,” the nature of pharmaceutical markets and the financial behemoth they represent often cause analysts to consider them separately from fine chemical manufacturing, such as that used in dye making or as fuel or plastic additives.

Definitions. The definitions of “chemical research,” “biotechnology,” “chemistry-based industries,” and even “the chemical industry” can be, and are, hotly debated. No matter how we define these areas now, it is agreed by many that the changes that we will see in the next two decades will so revolutionize our industry that it will not seem recognizable to a visitor from the year 1999. We will address here the impact that biotechnology and bioprocessing will make, since this will create new definitions for what will be a “new” industry.

The coming decade

The maturation of technology from scientific breakthroughs to commercial application follows the same kind of growth as micro-organisms. The long research and development cycle leads to implementation at small scales followed by large scale, mature production. Biotechnology, as we are seeing it applied today, had very few applications after the seminal discoveries about 1974. In the 1980s, the health industry, particularly pharmaceuticals, found value in the technology and began to employ it extensively. Now several biotechnol-



ogy-produced pharmaceutical products are entrenched in production. Large-scale commodity food chemicals such as ethanol, high fructose corn syrup, citric acid, and amino acids also employ microbes or enzymes. However, the inroads into commodity chemical production lags far behind these other chemical applications. Therefore, in an overall sense, biotechnology, in many aspects, is still in its infancy and growing like a teen-age youth in other areas.

It is clear that the use of biotechnology has not been fully realized. Even so, the industry still boasts some very impressive facts vis-à-vis societal and financial impacts.

- In 1999, the biotechnology industry accounted for \$13.4 billion in sales and \$18.6 billion in revenues.
- There are over 1,280 biotech companies in the United States.
- The industry represents a \$97 billion investment market, employs more than 153,000 people in high-wage, high-value jobs, and accounts for over \$9 billion in research and development.
- There are more than 90 biotechnology drug products and vaccines helping more than 200 million people worldwide.
- Biotechnology is responsible for hundreds of medical diagnostic tests.
- Biotechnology has brought nutrition and health improvements to foods such as corn, soybeans, tomatoes, carrots, and peppers.
- Biotechnology has augmented the efficient and effective clean-up of hazardous wastes and spills.
- DNA fingerprinting is a biotech process which has dramatically improved criminal investigation.

In the health-related fields where biotechnology has had its greatest commercial impact, cause-oriented groups tend to raise fewer problems — everyone is in favor of technology that delivers life-saving therapies. Thus the development of cancer fighting “biologics,” i.e. protein and nucleic acid therapeutics, has been widely heralded. Of importance to the “chemical enterprise” and chemical research is that this acceptance has created a commercial incubator for techniques that are being and will continue to be applied to, and transform, even the “core” chemical industry. These successes, combined with advances in the basic sciences underlying biotechnology, are already being felt. These include advances in aspects of the industry that are commodity-driven, ranging from soaps and detergents to textiles and “synthetic” fibers. These advances also embrace “green chemistry,” which is driven by energy and environmental concerns. As energy and/or environmental factors, including global warming and the carbon cycle, are increasingly emphasized, it is hard to see how any part of the industry will be unaffected, from desulfurization of fuels to bio-remediation of wastes, from steel production to ore refineries.

Such optimistic and glowing generalizations must, of course, be backed by concrete examples. The literature, e.g. *Trends in Biotechnology*, *Biotechnology Progress*, or *Biotechnology & Bioengineering* (the highest impact factor journal in biochemical engineering for the past three decades) and international journals such as *Nature Biotechnology*, is replete with promising ideas to replace traditional synthetic chemistry with biotechnology-based chemistry, e.g., “plants as factories,” combinatorial phage display, and abzymes, synzymes, and “newzymes” (enzymes altered to have unique catalytic properties). Already the term “metabolic engineering” is replacing “genetic engineering” and “functional genomics” is replacing “genomics” as common buzzwords. Chirality is all-important in the field of health-care products, and enzymatic chiral resolution, although by no means new, is a prime application for new biocatalysts.

Driving forces for biocatalyst development

Four major forces drive biocatalyst technology in “chemical-based” industries.

1) *Societal forces* — Society is constantly demanding new technologies, new products, and new ways of living. Examples include health products such as biosensors, tissue plasminogen activator (TPA), and Epogen®, and commodity items such as stain-removing detergents, preworn-looking blue jeans, and reduced-calorie food products. Society also demands that technology development includes minimal environmental impact.

2) *Business forces* — Profit/cost reduction drives many of the new changes. Will a biocatalyst give the same, or better, product at a lower cost? Are there good solutions to the problem of the high cost of isolating bioproducts in downstream processing? Active efforts in bioseparation systems are being undertaken to drive down the cost of biocatalysts to make them competitive with classic inorganic/organic catalysts. Also, business and economic demands are now requiring that better technologies be developed for selection and production of relatively cheap enzymes.

3) *Government-, regulatory-, and “cause”-driven forces* — Concerns about “greenhouse gases,” especially CO₂, will drive new “closed carbon cycle” methods, e.g., fine organic chemicals produced by metabolic engineering of crops. High laurate canola and corn are examples of how agricultural approaches to using whole organisms as biocatalysts create a product that would be energy intensive and likely yield more greenhouse gases if it were produced from petroleum (this postulate is still being evaluated by life cycle studies but generally appears to be true). The issue of genetically modified organisms will likely lead to regulatory pressures to completely characterize biocatalysts for efficacy and safety. Government policies already favor the use of biocatalytic processes for

producing fuel ethanol, but such policies could change.

4) *Basic research pressures* — Significant industrial and practical technologies result from the search of basic science for truth and discovery. These “just because it’s there” discoveries often lead to huge advances or potentially impactful advances. Examples include polymerase chain reaction (PCR) technology, which was designed for multiplying minute quantities of genetic information for research purposes but is now employed to produce useful genetic libraries for plant, animal, and microbial species or for forensic diagnostics. DNA sequencing was designed to help researchers decode genetic information, but with the advent of improved methods, the sequencing of the human genome and other important crops and species could lead to new health therapies or improved crop production. Genetic engineering was initially formulated out of a desire to understand how to transfer genetic information amongst similar microbial species. Now it is used to produce life-saving therapeutics such as insulin or human growth hormone, but can also be used to increase milk production in cows, manufacture new polymers, or develop new therapeutics. The following recasts these drivers in an outline that displays some of the specific aspects of each of the drivers.

Major Forces Driving Chemical Biotechnology

New Products (Societal Pressures)

- Health
 - Glucometer, Analysis
 - TPA, Epogen
- Commodity
 - Soaps and Detergents
 - Whey
 - Biodegradable plastics

“Discovery” or Basic Research (Technological Pressures)

- Genetic Engineering
- Site-directed Mutagenesis
 - Combinatorial / Phage Display
 - Combinatorial Chemistry and Biocatalysis
 - PCR
 - Fusion Proteins
 - Synzymes / Abzymes / Newzymes
 - Metabolic Engineering

Environmental (Regulatory & Legal Pressures)

- “Green Chemistry”
- Energy
- Greenhouse Effect

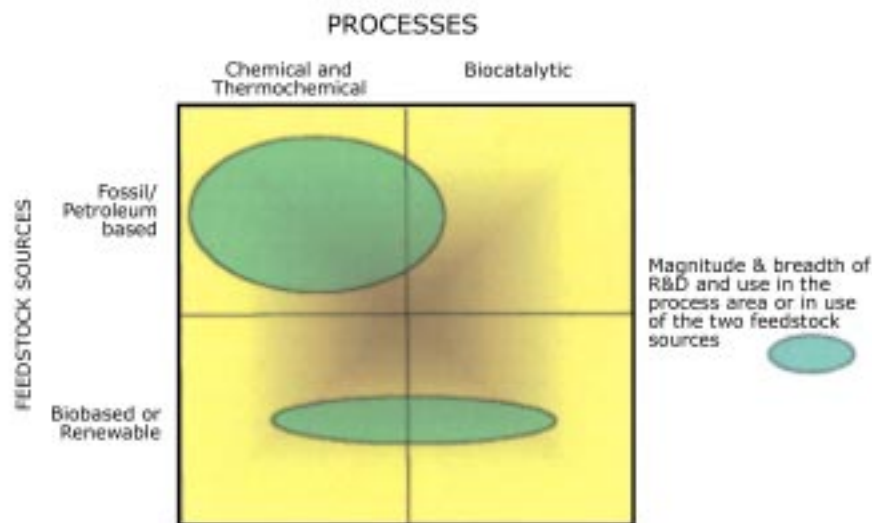
Profits/Cost Reduction (Business Pressures)

- Bioseparations

“Fine chemical makers are increasingly using enzymatic methods to make chiral intermediates” headlines an article in the major trade journal of the chemical industry, *Chemical & Engineering News* (Jan. 4, 1999). The article then points out that, “Fermentation and enzyme-based synthetic catalysis are starting to challenge traditional synthetic methods of producing optically active pharmaceutical intermediates. As these biocatalytic methods gain ground, a few organic chemistry-based intermediate manufacturers have climbed aboard, but not many seats remain for the rest.”

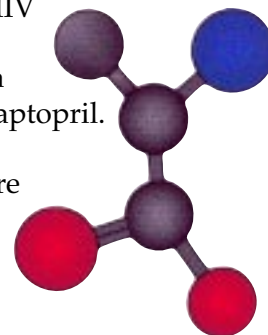
Biocatalysis has a large impact in the chemical world. The enzyme market alone is a \$1 billion global business. Traditionally, microbial and enzymatic processing have been used to convert biologically-derived (or renewable) feedstocks. However, they are increasingly being used with materials derived from fossil fuels. Uses are as divergent as chiral enzymatic transformations within an organic synthesis for a drug or for microbial desulfurization of diesel fuels. This more holistic view of the current chemical world is shown in Figure 1. It suggests the potential and challenge of applying biocatalysis to all feedstreams.

Figure 1: One view of the chemical world



Since pharmaceutical manufacturers are among the major customers of fine chemical manufacturers, the synthetic organic chemical industry will be impacted and transformed by the revolution in biocatalysts. Examples include production of precursors for Glaxo Wellcome's HIV drug, Ziagen, and DSM's Fine Chemicals production, including intermediates for aspartame, amoxicillin, and a variety of classical pharmaceuticals, e.g., diltiazem and captopril.

Many other examples of enzymatic routes to chemicals are listed in Table 1. The application or use noted in the table demonstrates the wide use of biocatalysts. One also



needs to note the modest use of biocatalysts within certain industrial sectors such as commodity or intermediate chemicals production.

In addition, the use, and potential use, of biocatalysts, whole cells, and phytochemicals have caused the appearance of a whole set of new companies dealing with biotransformation. Many, many companies are based on the paradigm of a nursery of small research-based start-up companies feeding into larger established firms.

Table 1: Novel microbial enzymes

Product	Enzyme	Origin
D-Amino acids (CF)	D-Hydantoinase	<i>Pseudomonas putida</i> , <i>Bacillus</i> sp.
	D-Decarbamoylase	<i>Blastobacter</i> sp., <i>Agrobacterium</i> sp.
L-3,4-Dihydroxyphenylalanine	β -Tyrosinase	<i>Erwinia herbicola</i>
L-Serine (CF, H)	Serine hydroxy-methyltransferase	<i>Methylobacterium</i> sp.
Acrylamide (Ch)	Nitrile hydratase	<i>Rhodococcus rhodochrous</i>
Nicotinamide (H)	Nitrile hydratase	<i>Rhodococcus rhodochrous</i>
Acrylic acid (Ch)	Nitrilase	<i>Rhodococcus rhodochrous</i>
Nicotinic acid	Nitrilase	<i>Rhodococcus rhodochrous</i>
2S,3R-3-(4-Methoxyphenyl-glycidic acid) methyl ester	Lipase	<i>Serratia marcescens</i>
Carbacephem (H)	o-Phthalyl amidase	<i>Xanthobacter agilis</i>
Chiral epoxide	Alkene monooxygenase	<i>Nocardia corallina</i>
R-2-(4 Hydroxyphenoxy) propionic acid (Ch)	Hydroxylase	<i>Beauveria bassiana</i>
S-p-Chlorophenylethanol	Alcohol dehydrogenase	<i>Rhodococcus erythropolis</i>
Chiral 2,3-dichloro-1-propanol	Halohydrin hydrogen-halidelyase	<i>Alcaligenes</i> sp., <i>Pseudomonas</i> sp.
S-1,2-Pentanediol	Alcohol dehydrogenase and reductase	<i>Candida parapsilosis</i>
D-Pantoic acid (H)	Lactonase	<i>Fusarium oxysporum</i>
Theobromine (CF)	Oxygenase	<i>Pseudomonas putida</i>
Adenosylmethionine (H)	Adenosylmethionine synthetase	<i>Saccharomyces sake</i>
Adenosylhomocysteine (H)	Adenosylhomocysteine hydrolase	<i>Alcaligenes faecalis</i>
Adenine arabinoside	Nucleoside phosphorylase	<i>Enterobacter aerogenes</i>
Ribavirine (H)	Nucleoside phosphorylase	<i>Erwinia carotovora</i>
5-Methyluridine	Nucleoside phosphorylase	<i>Erwinia carotovora</i>
Arachidonic acid	Multistep conversion	<i>Mortierella alpina</i>
Eicosapentaenoic acid	Multistep conversion	<i>Mortierella alpina</i>

[adapted and reprinted from *Trends in Biotechnology*, Vol. 17, 1999, Ogawa, J. and Sakayu Shimizu, "Microbial enzymes: new industrial applications from traditional screening methods, pp 13-20, Copyright 1999, with permission from Elsevier Science.] CF - commodity food; H - health related; Ch - chemical product or intermediate.

Other examples

The Presidential National Medal of Technology, the highest honor given in the United States for achievement in science and technology, was awarded to Amgen, a major U.S. biotechnology company, for bringing to market two widely successful medicines, EPOGEN™ and NEUPOGEN™. These two medicines vastly improve the quality of life of patients with cancer or kidney disease.

The chemical process industries are beginning to realize that enzymes are not only effective for catalyzing reactions of “natural” compounds within living systems, but that they can be used to catalyze reactions of “unnatural” compounds. Enzyme biocatalysts are being applied in the production of fine chemicals, pharmaceuticals, and agricultural chemicals. Their attractiveness comes from high selectivities, ability for use under ambient conditions, and ease of disposal.

The enzyme nitrile hydratase from a *R. rhodococcus* strain has been developed for the hydrolysis of acrylonitrile to acrylamide for use in plastics. The enzyme is immobilized in whole cells and can produce acrylamide concentrations greater than 600 g/L. The biocatalytic approach has reached a production level of 100,000 tons/yr.

The DSM-Toyo Soda process uses the enzymatic protease thermolysin for manufacture of aspartame, and is illustrative of two types of biocatalyst selectivity: chemical and stereoselectivity.

High-fructose corn syrup produced in large quantities (23 million tons in 1998) is an enzyme-based product. The process includes three enzymatic steps: the α -amylase catalyzed liquefaction of corn syrup, further hydrolysis of sugar oligomers by glucoamylase, and the isomerization of glucose to the glucose-fructose mixture.

The hydrolysis of penicillin G or V to 6-aminopenicillanic acid (6f-APA) using penicillin acylase is an early success story for the use of enzymes in chemical manufacture. Almost 9000 tons of 6f-APA were produced worldwide in 1995, mostly via the biocatalytic approach.

DuPont and Genencor have filed patents for processes and microorganisms to make 1,3 propanediol (1,3-PD) by fermentation in one step from various carbohydrate sources. The 1,3-PD is used in the production of the polyester polytrimethylene terephthalate.

Cargill-Dow Polymers is developing a large-scale fermentation process alongside their other corn processing systems followed by chemical processing (a type of biorefinery) to generate polylactic acid for a multitude of applications including biodegradable sutures, biocompatible fibers, packaging, and functional replacements for commodity plastics such as styrene.

Many researchers in academia, industry, and government are developing directed molecular evolution to produce enzymes with novel functions. The technique uses mutagenesis and DNA shuffling to generate random mutations in the genes of interest. This approach can increase the activity of selected enzymes by more than 100-fold over the native enzyme.

Novel enzymes derived from extremeophiles represent an area of high research and commercial interest. These enzymes have gained attention because they evolve under circumstances that can provide activity over a broader range of conditions. Enzymes (native or evolved), along with microbial catalysts, are used combinatorially to discover new biologically active molecules or to improve lead candidates for pharmaceutical discovery.

The timeline problem in roadmapping: “How do we get to 2020?”

Biocatalysis can have a broad impact in multiple aspects of the chemical industry. Biocatalysts can offer multiple advantages as described above, but to gain these advantages, biocatalysis and its application bioprocessing need to become a predictable and “routine” tool for conversion. The development of biocatalysis should be seen as adding processing and catalytic tools to the more traditional chemical and thermochemical methods of converting one chemical or material into a new and more valuable material.

We need to find ways to expand the utility and impact of biocatalysts by eliminating the typical difficulties or operational limits encountered in biocatalysis, such as temperature, pH, product inhibition, slower rates, and processing dilute aqueous product streams. This must all be accomplished while maintaining the advantages of high specificity and multi-step processing. High specificity allows precise reactions to occur (e.g., removal of organosulfur from diesel). Similarly, multistep processing improves yields both by elimination of intermediate synthetic steps and by decreasing solvent switching, thus reducing the number and volume of waste streams.

The bioconversion industries are in an explosive stage of development. Much of the root cause for this current state of excitement has been technology-driven. The technology has pulled the markets into new areas. In particular, with the more widespread use of biotechnology tools, the health industries have now become largely market-driven. Moving the larger scale bioprocesses from a technology pull to a market-driven basis is a continual challenge. Achieving market pull in the commodity chemical business will require new approaches and tools, a track record of reasonable successes and, in many cases, the creation of new markets. The formation of CargillDow Polymers, LLC is an example of a joint effort between the producer of corn syrup sugar-based lactic acid, Cargill, and

the product development company, Dow Chemical, which is devising methods to convert lactic acid into commercially viable products. DuPont's plans for 3-carbon polymers based on 1,3 propanediol includes the temporary use of a pure chemical process to establish the market while a biocatalyst-based process is commercialized. These ventures indicate that the biocatalysis area is moving to a market-driven mode that actively pursues and seeks out new technologies for exploitation rather than waiting for them to be offered. The industry involvement and excitement at this workshop reflected this point.

How do we reach these goals? One perspective views biocatalysts as just another catalyst possessing commercial perspectives of being "faster, cheaper, better" (Table 2). This perspective requires that the R&D of biocatalysts be directed towards reducing the time to market and implementation. This perspective demands implementation of recent biotechnology tools as well as development of new innovations.

Table 2: A simple industrial perspective on goals for biocatalyst development*

Operational Objective	Competitive Imperative	Development Time for Catalysts			Tools Needed to achieve FOM
		Current Chemical Varieties	Current Biocatalysts	Biocatalyst of the Future	
Faster	Speed to Market	2-5 years	10 years	2-3 years	Enzyme recruitment
Cheaper	Cost to Manufacture	\$1-10/kg	\$10-100/kg	\$1-3/kg	
Better	Range of Products	Broad	Narrow	Broad	

*Oral presentation by Genencor and Eastman Chemicals at NIST-ATP workshop, an industrial partnering, Boulder, CO, October, 1996.



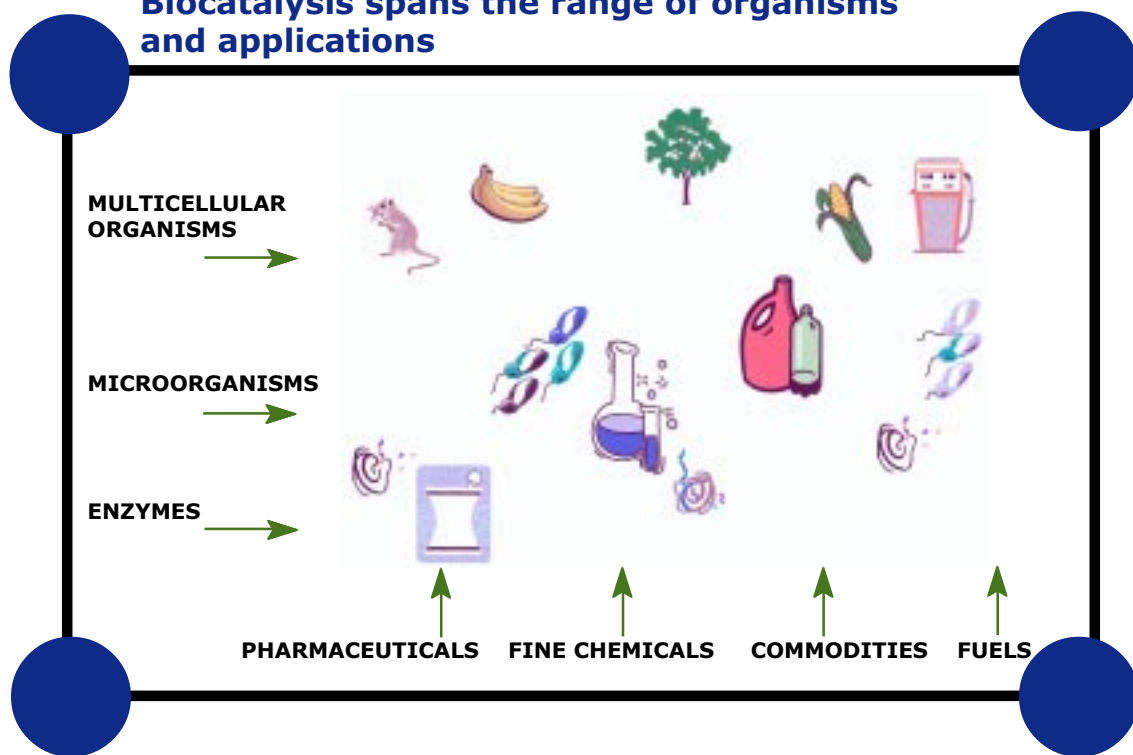
In this roadmapping exercise we used a model that involved two interlocking modes for categorizing biocatalysis. One axis is comprised of types of biocatalysts.

- Enzymes
- Microorganisms
- Multicellular Organisms (e.g., plants or animals)

The other axis is comprised of the product type that is largely a function of scale of production (ordered from low volume to highest)

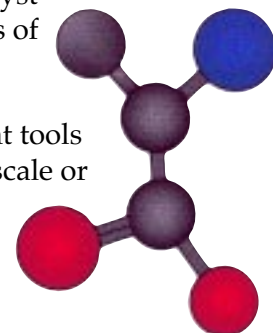
- Pharmaceuticals
- Fine Chemicals
- Commodities
- Fuels

Biocatalysis spans the range of organisms and applications



Unfortunately, each of the intersections between biocatalyst type and product is at a different state-of-the-art in terms of available R&D tools as well as production levels.

In addition, certain classes of discovery and development tools have broad applicability across all categories of process scale or tool requirements, for example:



- Screening and selection of biocatalyst
- Biocatalyst development and engineering
- Integration into larger processes (including separations)
- Modeling (both on the molecular scale and the process / economic scale)

These different scales of production, biocatalyst type, developmental state-of-the-art, and feedstock source create a complexity that requires simplification in order to allow formulation of R&D priorities and targets.

The workshop approached this complexity by dividing into work groups to tackle four basic areas, which possessed significant differences. These breakout groups were derived by creating categories which mixed the two axes noted on the previous page in a manner that would yield the greatest level of focus, impact to specific industries, and results that would be useful for strategic planners within agencies, industry, and other institutions. The four categories are defined as follows:

- A. Small volume bioprocessing
(fine chemicals, pharmaceuticals)
- B. Industrial processes (Large volume chemicals, materials)
- C. Screening/Selection/Development of biocatalysts
- D. Multicellular organisms as biocatalysts

A simple linear timeline cannot be constructed to describe or guide biocatalyst development. Not unexpectedly, the process will be complex and iterative with projects at various stages of development. For example, in the use of whole cells as biocatalysts, biopolymers such as α -hydroxypolyesters are well along in development. Similarly, the use of biomass in liquid fuel production has made its way into commercial use but continues to face many hurdles, despite Presidential and Congressional support to elevate it to a “national priority.” It was reassuring to find significant areas of concurrence among the four groups as to basic approaches to maximize the future use and value of biocatalysts.

The workshop process

Step 1. Defining Goals for 2020 and Beyond

The workshop participants were exposed to a range of possible goals in defining barriers and research priorities. One of these goal sets included a reduction of energy consumption and a decrease in adverse environmental impacts. The American Institute of Chemical Engineer’s Center for Waste Reduction Technologies has developed some measurable goals:

Widespread use of biocatalysts would lead to a 30% reduction in the chemical industry’s material intensity,

water consumption, energy intensity, toxic dispersion, and pollutant dispersion.

Performance metrics were also laid out as goals. Table 2 depicts one possible model. Additional concepts such as those outlined below were also considered:

- Increasing temperature stability of enzymes up to 120 - 130°C
- Increasing activity by 100 - 10,000 fold over current levels (in water or organic solvents)
- Productivity increases of 10 - 100 fold
- Enzymatic turnover rates comparable to current chemical catalysts
- Lifetime durability of months to even years
- Increasing numbers of types of enzymes employed (i.e., expand tool boxes to include isomerases, transferases, oxidoreductases, lyases, and ligases)
- Improving robustness of enzymes or microbes under immobilized conditions
- Molecular modeling allows *de novo* design of enzyme function in months instead of years

The workshop participants developed more specific performance goals relating to the individual focus of each breakout group. A compilation or summary of the goals of each focus breakout group is found in Appendix A. A consolidation of these goals is described below.

1. Biocatalysts will need to be produced more cost-effectively (cheaper) and address a wider range of chemical reactions in order to impact a broader range of uses.
2. Biocatalytic systems need to be as viable an option for process chemists as chemical catalysts are today.
3. Biocatalysts should be able to address a reduction in the impacts on water, materials, and energy consumption and contribute to reductions in toxics and pollutant dispersion. Impacts on carbon management should be positive, i.e., help reduce carbon emissions and possibly participate in carbon sequestration.
4. Biocatalysis and biocatalyst systems are, and should continue to be, part of the green chemistry movement.
5. More investment and attention should be given to discovering and using better tools for biocatalyst development.

The participants in all four work groups independently determined that **biocatalysts will need to be "better," i.e., more cost-effective and/or yielding more desirable products** than current catalysts if they are to

displace synthetic catalysts which have a very highly established market position. All four groups were united in this, although they differed subtly in what measures to employ in judging that the goal had been reached. A good synthesis of their views is that biocatalysts should be competitive in most areas with a target of 20% "better" while replacing 20-30% of traditional processes with biocatalysis-based processing. Similarly, 50% of all new processes should be bio-based. With international petroleum supplies erratic in cost and unreliable in crisis situations, many of these new chemical processes will be bio-based. **Bio-based industries utilizing biocatalysts will also be imperative for carbon sequestration and energy conservation** to address greenhouse concerns as well as environmental pollutant issues. Equally, the public perception of "natural is better" provides marketing and profit incentives for creation of a booming green chemistry industry utilizing biocatalysts. Life-cycle analyses will be needed to characterize contribution and impact of biocatalytic-based processes.

Unfortunately, the public does not understand the relationship between a benign green chemistry industry and the essential development of biotechnology / genetics engineering to achieve green chemistry in a viable and robust fashion. **The development of biocatalysts should be quickly promoted as an extension of green chemistry.** Likewise, the benefits of genetically engineered enzyme catalysts to address environmental problems need to be clearly communicated.

There was unanimity among the participants **that development of a "toolbox" of biocatalysts** is needed. True, many success stories of specific industrial applications of biocatalysts are available, but their success is not widely known nor are they sufficiently numerous. One of the essential goals is to fill the toolbox with

- New biocatalysts and new biocatalytic systems, per se.
- Methods to speed the development and production of biocatalysts.
- Systems that decrease the research and development costs.

One approach would be to have a better understanding of biocatalyst / enzyme mechanisms at a basic science level. Another is to increase screening and selection of appropriate biocatalysts using our current knowledge base, i.e., an empirical development approach. Almost certainly both approaches will be needed to fill our toolbox.

Specific goals of individual work groups include reduction of biocatalyst development time by a factor of 5-10. The development time of new whole cell biocatalysts should decrease from 10 years now to 2 years or less by 2020, and the production cycle for biocatalysts created by protein engineering should become as short as 3-6 months.

Step 2. Identifying Technical Barriers

Technical barriers for each of the four groups were also identified. The five highest ranked barriers are listed for each of the four groups in Table 3, below. This analysis displays the broad agreement among the groups on a few common problems such as the lack of a wider availability of biocatalyst types; the lack of adequate tools to work with screening, selection, development, and use of biocatalysts in process systems; inadequate understanding of enzyme or biocatalyst functionalities, operational parameters, stability, rates, selectivity, etc.; and, cost competitiveness of biocatalysts.

Table 3: Technical and Other Barriers Ranked from Highest Priority to Lowest (five per working group were listed, others are identified in the more detailed description in Appendix A). The scoring was not statistically different between the items where the box is colored the same: **Blue box-Highest priority; Green box-Medium priority; Yellow box-Lower priority**

A - Fine Chemicals/ Small Volume	B - Industrial Processes/High Volume	C - Screening, Selection, Development	D - Whole Organisms
Limited toolbox of possible conversions, modeling tools, immobilization techniques, facilities, new manipulation techniques, etc.	Limited numbers of suitable conversion reaction possibilities	Lack of understanding of enzyme or biocatalyst functions to permit improvements: Selectivity, Rates, Stability	Lack of sophistication in understanding metabolic engineering
Cost competitive economics	High cost of cofactors - currently no way to bypass their use	Lack of tools or methods to manipulate biocatalyst activities in a process	Lack of wide assortment of host systems - need more and better characterized systems
Assays for enzyme product and screening	High downstream processing costs in biocatalysis	Inadequate tools for screening, selection, and development efforts	Limited genetic transfer systems for plants and unusual organisms
Overcoming stability and activity issues	Cost competitive economics	Cost of this kind of research is high	Need better fermentation technology that is lower cost and innovative
Integration within process development scenarios	Discovering new catalysts is too slow. Cross disciplinary skill sets needed are rare	Effective production of enzymes from whole organisms	Insufficient links between chemistry and biology and inadequate informatics tools

While the four work groups were in broad agreement on a range of overarching goals, greater differences occurred in identifying specific technical barriers and research needs. The areas where needs/barriers were similar related chiefly to achieving the shared goals; the areas of difference related to the distinctive aims of each group and the character of the portion of the industry they were addressing. No attempt was made to normalize rankings across groups. Hence, rankings only provide a sense of what is important in each group rather than an absolute prioritization.

Common problems

The following are problems/barriers identified by the conference.

Lack of a biocatalyst inventory. The number of biocatalysts currently being employed, or those in the later stages of development, is unknown. Many commercial applications are trade secrets. However, the perception is that the toolbox is very sparse indeed. In addition, we are not certain what types of biocatalysts are needed. Thus an analysis of which biocatalysts are most urgently needed is in order. Agreement between all of the work groups exists on the following points:

- the **number and type of industrially significant reactions** catalyzed by biocatalysts needs to be increased
- **cofactor use and regeneration** are limiting the number of reactions that can be successfully catalyzed using biocatalysts
- **new biocatalysts need to be developed which are aimed at particularly useful and economically valuable transformations**, e. g., selective oxidations.

In addition, a second kind of toolbox inadequacy was identified. This toolbox involves **tools that assist in the operation and use of biocatalysts in process systems**. This toolbox was also judged to be inadequate. Lastly, in whole organisms, the working group strongly noted that **an understanding of the metabolism of whole organisms and how to engineer those metabolic pathways** is very high on the priority list in order to employ whole organisms as biocatalysts.

Public education. The work groups unanimously determined that positive public perception of biotechnology and biocatalyst development is inadequately addressed. While most of the goals and barriers discussed were technical, many non-technical issues will affect the ability for R&D biocatalyst development. Public support, and more specifically, support by opinion makers, managers and legislators will be needed. Specific goals include the incorporation of biocatalysts in basic chemistry curricula and the inclusion of an adequate component on biocatalyst development, production and application in all catalyst courses. Additionally, the broader public needs to be informed of the benefits of biocatalysts in the biotechnology arena as well as the simple basics of biocatalysis.

Step 3. Identifying Research

Each working group was asked to identify the top 10 research needs within their area of discussion. Again, a comparative summary is compiled and shown in Table 4, next page, for six of those top research priorities. No attempt was made to normalize rankings across groups. Hence, rankings only provide a sense of what is important in each group rather than an absolute prioritization. The full outline of the research needs identified for each of the four working groups is found in Appendix A.

Step 4. Research Implementation

Each group was asked to outline how they envisioned the implementation of their recommendations would occur and, in some cases, how they would track the success of the recommendations in the roadmap. Only three of the groups were able to accomplish this step. The outlines of those recommendations are found in Appendix A. We have taken those recommendations and crafted a separate implementation section of this report. This section includes most of the relevant suggestions provided by the workshop participants. Those that were not specifically included are not inconsequential, but are considered to be options for any of the specific implementation recommendations made in this report.

Table 4: Specific Technical Research Needs Ranked from Highest Priority to Lowest (six per working group were listed, others are identified in the more detailed description in Appendix A). The scoring was not statistically different between the items where the box is colored the same: **Blue box-Highest priority; Green box-Medium priority; Yellow box-Lower priority**

A - Fine Chemicals/ Small Volume	B - Industrial Processes/High Volume	C - Screening, Selection, Development	D - Whole Organisms
Identifying contents of biocatalyst developmental toolbox	Discovering and developing new catalysts in all 6 biocatalytic domains (hydrolases, isomerases, transferases, oxidoreductases, lyases, and ligases)	Develop tools for computational biology to develop better descriptions of enzyme mechanisms	Improve understanding of metabolic pathway engineering and develop better tools for probing metabolism of whole cells
Developing mediators and electrodes for electrically coupling enzymes (including photo-chemical)	Develop economic approaches to bypass cofactor requirements	Develop biocatalyst arrays on chips to enhance rapid screening potential	Design and characterize more and more varied host systems
Integrating the discovery, process development, and economics of biocatalytic processes	Understanding new enzyme structure/function	Develop biocatalytic tool boxes for use of biocatalysts under variable operational conditions	Be able to undertake directed evolution at the whole cell level
Achieving high activity of non-hydrolytic enzymes in polar organic solvents	Developing more stable biocatalysts via chemical or other stabilization methods	Creation of high-quality, functional genomics libraries	Develop robust and useful tools to probe metabolism, improve selection, create metabolic switches, etc.
Finding the minimum peptide scaffold for biocatalysts (including defining catalytic sites for or by biomimetics)	Lowering the cost of biocatalyst production	Increase understanding of enzymology in non-aqueous environments	Develop pools of poised organisms suitable to address new needs
Real time assays for high throughput screening	Integrating upstream and downstream processing in biocatalytic processing systems	Design and develop better catalysts to introduce oxygen functionality on hydrocarbons	Identify desirable traits that allow for enduring extreme environments, breaking species barriers, etc.

How do we get to 2020? How far are we? What will it take to get there?

A. Goals and Objectives

The goal of the roadmapping effort was to acquire sufficient information and input to craft an R&D pathway for the development of biocatalyst technology for applications in the broadest definition of the chemical industry. This definition includes the production of commodity, intermediate, and fine chemicals, ranging from basic chemicals to pharmaceuticals and using both conventional and unconventional feedstocks. Conventional implies petroleum or coal-based feedstocks. Unconventional includes renewable biomass, natural gas, using gases such as carbon dioxide or nitrogen, other inorganics, and feedstocks from marine environments (i.e., sulfur compounds). Sufficient information was obtained to initiate the construction of a first-generation, biocatalysis roadmap.

The implementation section of this document outlines a recommended strategy to facilitate and promote the development of biocatalysts in support of this roadmap. As R&D progresses, specific performance indicators will appear that will serve as markers of true progress.

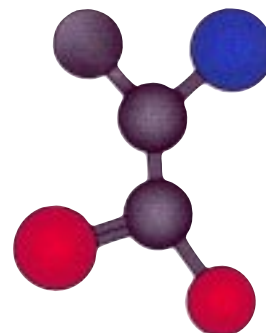
B. Performance Indicators

1. Use of biocatalysts by process chemists will become as routine as the use of conventional catalysts. Biocatalysts will be viewed as reagents that can be obtained from a catalog (some are today) or ordered up from a biocatalyst development company.

- The range of environments for biocatalyst application will expand beyond simple aqueous systems into nonconventional, complex multiphasic or multimilieu environments.
- Biocatalyst function will become more predictable, particularly with respect to reactions catalyzed under the aforementioned conditions.

2. Biocatalyst development time (from design to synthesis to deployment) will become competitive with conventional catalysts.

- Functional platforms based on substrate, milieu, reaction, etc. will become available, from which it will be possible to rapidly screen and develop biocatalysts for tailored use.



3. Structure/function properties of biocatalysts will become more available. This will facilitate wider applications in industry for a wide range of biocatalyst substrates or feedstocks.

C. Strategy

The strategy has two components:

- 1) promoting R&D in biocatalyst research and use, and
- 2) monitoring the progress of biocatalyst development and deployment.

1. Promoting R&D Support. Steps will be taken to encourage federal, private, and nonprofit funding for biocatalyst development in support of the R&D identified in the roadmap. Areas of R&D interest and opportunity include:

a. Conventional processes (aqueous processing on small to medium-sized scales) for typical industries such as specialty and fine chemicals (pharmaceuticals) and in unconventional arenas such as commodity chemicals and petrochemical processing (organic media, gas phase, etc.). Organic media should not be specific to commodity and petrochemical processing, rather, it should be examined in all potential arenas.

b. Biocatalyst discovery and the need for additional resources for the design of new biocatalysts with optimized/tailored properties.

c. New avenues of biocatalyst use for processing renewable biomass resources, renewable gas conversion (carbon dioxide, nitrogen oxides, etc.), and other unconventional resources, e.g., inorganics. Included in this component will be the development of biocatalysts in unconventional hosts such as plants, animals, etc.

d. Tool development and fundamental understanding of biocatalyst structure and function. This will provide the critical technology to allow biocatalyst developers to make significant advances in the other two strategies.

Specific approaches to include more biocatalyst research in programs and R&D calls will require some tailoring of the information in the documents to the target audience among which will likely be industry, academia, and federal agencies. The approach for R&D organizations employing a programmatic plan to solve mission-oriented problems will require targeting the organizational program managers, the actual performers of

the research of that programmatic effort, and their stakeholders. For R&D organizations employing a solicitation process, the target will be those who craft such solicitations and the approach will be to have these solicitations reflect the portions of the roadmap that can logically and rationally be integrated into their solicitation(s). For R&D organizations with the mission of supporting principal investigator-driven, peer-reviewed work, the targets will likely be the academic and basic research community itself. This will require exposure of the roadmap concepts in public forums. Several industries that use biocatalysts, including chemical, agricultural, and forest products, have encouraged some federal funding agencies to support work in precompetitive research in areas with long-term benefit to their industry.

2. R&D Monitoring. A successful and productive implementation of the roadmap by research institutions will require that R&D recommendations be monitored for use within the research community and, in particular, within the chemical industry. This can be accomplished by tracking federal and private funding for biocatalyst R&D, new industry developments in bioprocessing, and new biocatalyst citations in the literature (see Table 1, page 14).

D. Approach

A two-fold approach is recommended to accomplish the above strategies. First, ownership for promoting the R&D identified within the roadmap will be determined. Second, mechanisms will be established to track and monitor biocatalyst R&D and deployment. Two areas that this approach will address include a trained work force and the current specifications of industrial processes. Many chemists and chemical engineers are still unfamiliar with biocatalysts and enzymes. This is changing but will not occur overnight. The approach involves educating this group of influential stakeholders. Also, 90% of commodity chemical processes involve organic solvents which is not the typical milieu for biocatalysts. In addition, these processes normally operate at temperatures and pressures much higher than is suitable for biocatalysts. This approach will seek to make inroads addressing this 90% market and also to enlarge the 10% of the market where water is present and biocatalysts are more likely to be active participants.

The approach involves all R&D sectors in the United States — industry, not-for-profit, academia, and government. The target audiences include all agencies that support biocatalyst R&D, industries and companies involved in biocatalyst development, and non-governmental organizations that would have an interest in the development of biocatalysts, especially organizations concerned about genetically-modified-organisms (GMOs).

1. Ownership. There is a need to identify a lead organization and to establish a mechanism for the interaction between the lead and other

stakeholders in this R&D arena. One approach is to form a biocatalyst executive steering group commissioned to further the strategies and objectives of the roadmap. Representatives to the steering group could be from other trade organizations or appropriate industry, academia, and laboratory personnel.

The Council for Chemical Research (CCR) has been active in support of the various Vision 2020 roadmaps and will be encouraged to establish a central role. The other signatories of the Vision 2020 compact will be enjoined to participate with roles commensurate with their interests and the interests of their stakeholders. For example, the American Chemical Society, Council for Chemical Research and the American Institute of Chemical Engineers might focus on promoting the roadmaps to academic, national laboratory, industry and other research institutions they each represent. The Chemical Manufacturer's Association and the Society of Organic Chemicals Manufacturing Association might represent corporate manufacturing interests. Additional representation will be sought from the Biotechnology Institute Organization (BIO), which represents the biotechnology industry and other trade and not-for-profit organizations.

2. Monitoring. A key to successful implementation of the roadmap is tracking R&D progress and monitoring R&D results. Biotechnology / biocatalysis funding through various federal agencies and departments, papers published in research journals, corporate R&D investments, venture capital investments, new company developments, new bioprocess applications, etc., are areas to monitor with respect to biocatalysis R&D progress and the general business health of biotechnology related to biocatalysts. Various for-profit, not-for-profit and federal organizations with experience in this type of tracking and monitoring work include the Rand Corporation, Biotechnology Industry Organization (BIO), the National Science Foundation (NSF), and others.

E. The Path Forward

The following activities are recommended to initiate and begin the focus on roadmap implementation:

- Establish an executive steering committee and convene one meeting of the committee (October, 2000). Representation to the committee should consist of chemical industry trade organizations as well as interested university, government, and not-for-profit groups.
- Make roadmap presentations to trade organizations and by trade organization to their respective members (April, 2001)
- Present papers in overview of the roadmap in professional meetings, conferences, etc. as a means of promoting the R&D identified (CY2001)

- Sponsor technical sessions at professional meetings, conferences, etc., containing R&D papers that address R&D areas within the roadmap (CY 2002)

F. Benefits to Users of Roadmap Information

The use of the roadmap by funding agencies, industry, and other R&D organizations should provide some increased awareness of both the challenges and opportunities that lie within the realm of biocatalysis. The introduction to this roadmap depicts the state-of-the-art and the ongoing R&D efforts in this field. The consensus that the field is ripe and that opportunities abound to harvest a rich supply of useful biocatalytic tools is widespread. The user of this roadmap will benefit from the broad experience of a multitude of scientists in the various fields of biocatalysis. Previous reports on biocatalysis have touched on various aspects of the opportunity. This roadmap can be a powerful tool in crafting requests for proposals, in outlining research programs, and in addressing specific biocatalytic development pathways.

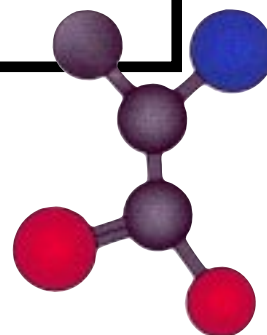
Successful implementation of the roadmap recommendations can be ensured through dedicated and committed support by the federal government and industry. This report can provide federal agencies with information and research challenges that will be useful in guiding their funding priorities and solicitations. In addition, we are hopeful that the report will also provide some information that is helpful in developing policy, particularly through establishing environments that encourage the rapid development of this particular arena in the wide world of biotechnology.



Implementing the R&D in the Roadmap

Potential success factors for implementing this roadmap in the chemical industry can be shown in several categories. The following success factors outlined by one of the working groups are germane for the entire workshop.

- A funding track: 10 times current by 2002 would be a measure of high success.
- New products to market. In the commodity chemical industry, there are only a handful of existing products that have been commercialized over the past 15 years. If this roadmap impacts the industry, the increase will be different for the pharmaceutical industry versus the broader chemical industry. For the pharmaceutical industry, if the rate of introductions of new products increased by 50% per year, success could be claimed. In the broader chemical industry, a three-to-five fold increase in new products employing biocatalysts would demonstrate a real impact.
- The establishment of oversight committees containing members of reputable organizations that monitor the use and development of biocatalysts, particularly involving GMOs, indicates success in implementing the tenets of the roadmap.
- Widely distributed success stories would be an obvious indicator of success.
- The emergence of influential champions in industry, government, or academia is an indicator that the roadmap's suggestions are being taken seriously by the chemical enterprise community.
- Simply tracking jobs, sales, improved economics in the chemical community as they are related to biocatalysis, would be a clear success indicator.
- Sessions involving biocatalysis at professional meetings, government project reviews, and in specialized meetings should increase if the roadmap recommendations are being implemented.



Goals

Group A - Biocatalysts for Fine Chemicals/ Small Volume Bioprocesses/Pharmaceuticals

Technical

- Increase **process intensification** or volumetric productivity: kg/capacity/time by 10 fold by 2000
- Shift one-third of processes from batch to flow reactors
- Improve catalyst cost/value contribution
- Increase number of products made by biocatalysts: 10% by 2010 and 20% by 2020, replace 30% of traditional processes with biocatalyzed processes; produce 30% of the value (\$) of fine chemicals by biocatalysts
- Develop robust biocatalysis toolbox that enables a paradigm shift and removes the distinction between bio and chemical catalysts
- Increase speed of development and production by a factor of 10
- Develop catalysts that carry out multi-step reactions

Educational, Policy or Other

- Change the approach to addressing chemical problems to include biocatalysts
- Develop new processes other than whole cell processes for production opportunities

Group B - Biocatalysts for Industrial Processes (Large Volume Chemicals/Materials)

Technical

- Biocatalysts will produce ~ 20,000 pounds product per pound of catalyst
Double value/volume of bio-based products every 5 years (from now to 2020)
- Processing costs will be less than conventional chemical catalyst
20% of chemicals and fuel products will be derived from biotechnology
50% of new chemicals will be based on bio-processing
- Design chemicals and processing that are intrinsically recyclable or biodegradable
- Develop bioproducts with same or better performance
- Make at least a 30% impact on the chemical industry's material intensity, water consumption, energy intensity, toxics dispersion, and pollutant dispersion

Educational, Policy or Other

- Use biocatalysis to recover carbon
- Improve public acceptance of biotechnology and products and product stewardship

Group C - Screening/Selection/Development of Biocatalysts

- Achieve 30% improvement in material, water and energy consumption and toxic & pollutant dispersion
- Develop methods for screening a biocatalyst/enzyme in 2 weeks
- Develop a catalyst with broad substrate specificity but retaining reaction, regio- and stereo-specificity
- Screen for a formulated process-based systems
- Functionally understand enzyme mechanisms
- Incorporate synthetic enzymes into bioprocessing
- Develop key skills for high throughput screening and heterogeneous processes that are consistent with the breadth of biodiversity
- Reduce research costs by 90% by reducing cycle time, etc.
- Make biocatalysts 20% better than commercial catalysts with
 - higher turnover
 - more robust
 - indifferent to feedstock
 - reduction in energy and waste

Group D - Use of Whole Organisms

This group did not outline goals with quantifiable measures. They provided a long, comprehensive list of desired traits, operational conditions, needs for increased numbers of characterized genetic systems, and other general items.

Appendix B:

The output from the November, 1999 meeting as compiled by Energetics, Inc., can be found on the Council for Chemical Research Vision 2020 website,

<http://www.ccrhq/vision/index.html>

The same site permits access to other Vision 2020 reports and to the chemical industry's basic visioning document, "Technology Vision 2020: The U.S. Chemical Industry."

New Biocatalysts: Essential Tools for a
Sustainable 21st Century Chemical Industry
November 16-18, 1999
Palo Alto, California

Affiliation as of November, 1999

Joe Affholter, Maxygen
William A. Apel, Idaho National Eng. & Env. Laboratory
Frances Arnold, Cal Tech
Patrick Bigot, Chevron Chemical
Robert Bloksberg-Fireovid, DOC, NIST/ATP
Peter Bluford, Sangamo BioSciences, Inc.
Marion Bradford, A.E. Staley Mfg. Co.
David Boron, DOE, Office of Industrial Technologies
Harold J. Bright, Office of Naval Research
Ross Brindle, Energetics, Inc.
Alle Bruggink, DSM Research
Douglas Cameron, Cargill, Inc.
Ellen R. Campbell, The Nitrate Elimination Company, Inc.
Chris Caperton, Energetics, Inc.
Joel Cherry, Novo Nordisk Biotech, Inc.
Doug Clark, UC Berkeley
Brian H. Davison, Oak Ridge National Lab
Sue Markland Day, Bay Area Bioscience Center
David R. Dodds, Bristol-Myers Squibb
Jonathan S. Dordick, Rensselaer Polytechnic Institute
Michael von Fahnestock, Battelle
James R. Frank, Argonne National Laboratory
Robert S. Glass, Lawrence Livermore National Laboratory
Randolph Greasham, Merck & Co.
Fred Hart, The Hart Partners Inc.
Michael E. Himmel, National Renewable Energy Laboratory
Nancy Ho, Purdue University
Gjalt Huisman, Maxygen
Larry Ito, Dow Chemical Company
Keith Jamison, Energetics, Inc.
Hank Kenchington, DOE, Office of Industrial Technologies
John Kerr, Lawrence Berkeley National Lab
Alan Klotz, Novo Nordisk Biotech, Inc.
Peter Lanciano, Altus Biologics, Inc.
Xiao-Chuan Liu, Austin Peay State University
Ripudaman Malhotra, SRI International
Shawna McQueen, Energetics, Inc.
Daniel J. Monticello, Energy Biosystems Corp.
Gene Petersen, National Renewable Energy Laboratory
Sun Ai Raillard, Maxygen
David Rethwisch, University of Iowa
Dan Robertson, Diversa Corporation
Sandra Russell, DuPont Central Research
William Scouten, USU Biotechnology Center
Robert G. Shong, Texaco Upstream Technology
Barbara Smith, Chevron Chemical
Jim C. Spain, Air Force Research Lab
Charles H. Squires, Dow Chemical Company
Emiel G. J. Staring, DSM Research
Pim Stemmer, Maxygen
Koni Stone, CS University, Stanislaus
William Stringfellow, Lawrence Livermore National Laboratory
Henry Talbot, Dow Chemical Company
Matt Tobin, Maxygen
Paris Tsobanakis, Cargill, Inc.
William D. Wilson, Lawrence Livermore National Laboratory
Alice Wright, CS University, Fresno
Richard T. Zvosec, Cargill, Inc.

Contact Information

For more information contact these
Council for Chemical Research members:

William Scouten, Dean, College of Sciences,
University of Texas at San Antonio
6900 North Loop 1604,
San Antonio, TX 78249-0661
210-458-4450
wscouten@utsa.edu

Gene Petersen, Chemistry for Bioenergy Systems Center,
National Renewable Energy Laboratory
1617 Cole Boulevard,
Golden, CO 80401
303-275-2994
gene_petersen@nrel.gov

“New Biocatalysts” Workshop Planning Group

Affiliation as of November, 1999

Co-chairs

Gene Petersen,
National Renewable Energy Lab

William H. Scouten,
Utah State University
Biotechnology Center

Members

Robert Bloksberg-Fireovid, NIST/ATP
David Boron, U.S. Department of Energy
Arindam Bose, Pfizer, Inc.
Doub Cameron, Cargill, Inc.

A. Stephen Dahms,
San Diego State University
Brian Davidson, Oak Ridge National Lab
Richard Willson, University of Houston

CCR Vision 2020 Bioprocessing/Biotechnology Work Group

Affiliation as of November, 1999

William H. Scouten, Chair, USU BTC
Robert Bloksberg-Fireovid, NIST/ATP
David Boron, U.S. Department of Energy
Arindam Bose, Pfizer, Inc.
Bryan Lawlis, Covance
A. Stephen Dahms, San Diego State University

Robert Dorsch, DuPont Life Sciences
Janie Fouke, National Science Foundation
Gene Petersen, NREL
Vincent Vilker, NIST
Richard Willson, University of Houston

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